CASE GY0053 NP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

PENDRI ET AL.

Art Unit: N/A

Examiner: N/A

APPLICATION NO: 10/734,012

FILED: DECEMBER 11, 2003

FOR: PROCESS FOR PREPARING THE ANTIVIRAL AGENT [1S-(1 ALPHA, 3 ALPHA, 4 BETA)]-2-AMINO-1,9-DIHYDRO-9-[4-HYDROXY-3-(HYDROXYMETHYL)-2-METHYLENECYCLOPENTYL]-6H-PURIN-6-ONE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

In the Specification:

Please enter the following amendment to the Specification, at page 43, line 24, which is made to correct a citation error.

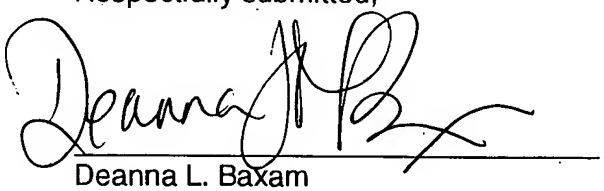
"In Process H, the homochiral bicyclic lactone of formula **49** can be used as starting material for the preparation of the compound of formula **52**, and can be prepared as described in [Corey et al. J. Med. Chem. 193, 36, 243] Miyaji, K. et al., Tetrahedron Letters, Vol. 32, No. 35, pp. 4557-4560, 1991. The bicyclic lactone of formula **49** can be treated with paraformaldehyde in a mixture of glacial acetic acid and sulfuric acid to add formaldehyde across the double bond. This treatment yields a diacetate of formula **50**. The diacetate of formula **50** is subsequently stirred with a base such as potassium carbonate in an alcohol solvent, *e.g.*, MeOH, to hydrolyze the acetate moieties and provide the diol of the formula **51**. The alcohol moieties of the diol of formula **51** can be protected as silyl ether groups by treating the diol with a silylating reagent of the formula $R^cR^d{}_2SiY$ (wherein R^c, R^d, "

A replacement Specification page reflecting these amendments is enclosed.

The citation on page 43, line 24 was incorrect and the correct citation is now included. This reference discloses a general procedure for the synthesis of homochiral bicyclic lactone, a starting material reflected in various schemes of the invention (e.g., Schemes 15 and 16).

No fees are believed to be due in connection with this response, if it is determined that any such fees are due, Applicants will promptly remit such fees upon receipt of an appropriate notification.

Respectfully submitted,



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compound of formula **56** can be further purified by, for example, silica gel chromatography.

The methylene compound of formula **56** serves as a suitable compound for coupling with a guanine precursor (purine compound of formula **28**, wherein X is Cl, Br or benzyloxy). For instance, the methylene compound of formula **56** is treated under Mitsonobu conditions with 2-amino-6-chloropurine to give the methylene compound of formula **57**. Preferably the Mitsonobu conditions comprise treatment with DEAD and triphenylphosphine. The methylene compound of formula **57** can be further purified by, for example, silica gel chromatography.

The conversion of the methylene compound of formula **57** to the compound of formula **21** can be completed by deprotection of the silyl ether moieties and hydrolysis of the 6-X group on the purine moiety. The two silyl ether moieties are cleaved by treatment with fluoride ion (*e.g.*, tetralkylammonium fluoride reagent such as tetrabutylammonium fluoride in THF) to give the compound of formula **39**. In embodiments of the process wherein the purine moiety has a 6-chloro or iodo group, the 6-halo group is hydrolyzed by heating the compound of formula **39** with aqueous base or acid, preferably aqueous base, *e.g.*, 2 N sodium hydroxide solution, to give the compound of formula **21**. In embodiments of the process where X is a 6-O-benzyloxy group, conversion to the 6-oxo group can be performed using acidic conditions, *e.g.* 2 N HCl. The compound of formula **21** can be further purified by, for example, silica gel chromatography.

In Process H, the homochiral bicyclic lactone of formula **49** can be used as starting material for the preparation of the compound of formula **52**, and can be prepared as described in Miyaji, K. et al., Tetrahedron Letters, Vol. 32, No. 35, pp. 4557-4560, 1991. The bicyclic lactone of formula **49** can be treated with paraformaldehyde in a mixture of glacial acetic acid and sulfuric acid to add formaldehyde across the double bond. This treatment yields a diacetate of formula **50**. The diacetate of formula **50** is subsequently stirred with a base such as potassium carbonate in an alcohol solvent, *e.g.*, MeOH, to hydrolyze the acetate moieties and provide the diol of the formula **51**. The alcohol moieties of the diol of formula **51** can be protected as silyl ether groups by treating the diol with a silylating reagent of the formula $R^cR^d{}_2SiY$ (wherein R^c, R^d,